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Effect of parenteral morphine on overall survival in patients with lung cancer

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Abstract

Aim: Terminal-stage cancer patients often receive parenteral morphine treatment (PMT) to relieve various symptoms associated with the progression or adverse events associated with cancer. Our study was aimed at a retrospective evaluation of the survival of patients with terminal-stage lung cancer who received inpatient PMT due to pain and dyspnea palliation.

Material and Methods: We carried out a retrospective analysis of 52 terminal-stage lung cancer patients who received PMT at our hospital. The patients were divided into three groups according to the indications for PMT: Group A (uncontrolled dyspnea; n = 23), Group B (pain; n = 22), Group C (both shortness of breath and pain; n = 7).

Results: Of the total, 23 (44.2%) received morphine for dyspnea, 22 (42.3%) for pain and seven (13.5%) for both. A good subjective response ("no symptoms" or "mild symptom") was documented in 46 patients (88.4%), poor response in four patients (7.4%) and no response in two patients (3.8%). The median survival time from the onset of PMT was 85 days (range 54–117 days). The study found dyspnea and pain to be indications for PMT in terminal-stage lung cancer patients, with dyspnea being the main indication for PMT. Patients in Group A (shortness of breath) required lower doses of morphine than in Group B (uncontrolled pain), although the survival time from the onset of PMT was significantly shorter in patients with dyspnea (Group A) than in patients without dyspnea (Group B).

Discussion: Further studies are required to facilitate the effective and appropriate use of PMT in terminal-stage lung cancer patients. Dyspnea was the major indication for PMT in terminal-stage lung cancer patients, and the survival time was considerably limited in this group.

Keywords

Morphine, Palliative Care, Survival

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Introduction

Lung cancer is the leading cause of cancer-related death, and its incidence is around the world is increasing. Lung cancer may, along with its treatment and accompanying conditions, cause a variety of symptoms that require palliation.

Pain is the leading symptom indicating a palliation need in cancer patients. Although the frequency of pain varies according to the stage of the disease, it is around 25-50% in patients undergoing early-stage and active cancer treatment, while this rate rises to 70–80% in metastatic patients [1]. Pain has not only negative physical effects on cancer patients, but is also associated with serious psychosocial effects in patients. [2]. The effective treatment of pain both increases the quality of life of the patient and strengthens treatment compliance, although adequate pain palliation cannot be achieved in one in three patients [3].

Shortness of breath is a frequently observed symptom in patients with lung cancer, particularly in the advanced stage, with a reported incidence during diagnosis of 19-64%. In the advanced stages of the disease, the rate is 32% on average, climbing to 90% in the final stages of life [4]. Appetite loss, sleep disorders, depression, anxiety disorders and, consequently, severe quality of life impairment are often observed in patients with these symptoms [5]. The compliance of the patient with cancer treatment and their self-care may be impaired in the presence of untreated pain and shortness of breath.

Opioids, including morphine and hydromorphone, are widely used for the control of moderate to severe pain and dyspnea in hospice and palliative care patients [6]. Opioids play a leading role in palliative care approaches, in which morphine is most commonly used, mostly injected intravenously or subcutaneously due to the inconvenience of intramuscular injections.

Although both the general public and health professionals believe opioid use will generally accelerate death, in fact, appropriate doses of opioids can significantly improve pain and shortness of breath and prolong the time to death. Several guides based on previous studies recommend parenteral morphine treatment (PMT) for the relief of uncontrolled pain and dyspnea in patients with terminal-stage lung cancer [7,8,9,10].

Our study presents a retrospective evaluation of the survival of patients with terminal-stage lung cancer who received inpatient PMT due to pain and dyspnea palliation.

Material and Methods

Patients diagnosed with terminal-stage lung cancer who received morphine (parenteral) treatment in the palliative care unit of our hospital between January 2017 and January 2020 were included in this retrospective-design study. Survival, as the primary endpoint, was evaluated as the time from the start of the morphine infusion to the date of death.

Data on the age, gender, histopathology, stage, first-stage treatment, comorbidities, pre-morphine opioids, and other analgesic and psychiatric drugs used by the patients were obtained from the available data. Morphine treatment was administered in two different ways, either as a continuous infusion intravenously (IV) or as intermittent subcutaneous (SC) injections every 4 hours.

Changes in vital signs, including respiratory rate, oxygen saturation, transient changes in systolic blood pressure up to 12 hours following the initiation of morphine treatment, and the presence or absence of side effects of morphine, delirium, sedation, and respiratory or cardiac depression were noted.

The study included patients with an Eastern Cooperative Oncology Group (ECOG) performance status of 3–4 who received PMT for uncontrolled dyspnea and pain. The patients were treated with a continuous infusion or subcutaneous injections of morphine for the relief of dyspnea and/or pain for the first time.

Each physician adjusted the doses as found clinically appropriate and provided concomitant palliative treatment (for example, oxygen and corticosteroids) for dyspnea.

Additional comorbidities of the patients (pulmonary embolism, insertion of drain due to pleurisy, regulation of treatment for pneumonia and COPD attack, application of palliative RT to the thorax and endobronchial procedures due to stenosis) were included in the study after stabilization with the necessary treatments.

The patients were evaluated in three groups:

Group A - Patients receiving morphine due to uncontrolled dyspnea

Group B - Patients receiving morphine for uncontrolled pain

Group C - Patients receiving morphine for both dyspnea and pain

The relationship between intragroup PMT and survival was investigated.

The exclusion criteria were: uncontrolled comorbidity, diagnosis of malignant mesothelioma, chronic obstructive pulmonary disease with hypercapnia, uncompensated congestive heart failure, and severe renal or hepatic failure.

The Visual Analogue Scale (VAS) is used to make a rapid (statistically measurable and repeatable) classification of symptom severity and disease control; however, it is often difficult to measure severe dyspnea and pain in end-stage patients with progressive respiratory failure as their symptoms may be so severe and may be progressing so rapidly that they can barely speak or evaluate their symptoms. We applied the scale only to patients who were able.

The Visual Analog Scale (VAS) is used to quantify values that cannot be measured numerically. The two end definitions of the parameter to be evaluated are written on both ends of a 100 mm line, and the patient is asked to indicate, which point along the line corresponds to their condition by drawing a line, placing a dot or simply by pointing. For example, for pain, one end of the line says “no pain” and the other says “very severe pain”, and the patients mark a point along the line corresponding to their present condition on the line.

VAS Rating: The mean of the values obtained for the patients was calculated as:

-0 point, no symptom

-1–2 points, mild symptom

-3–4 points, a little greater symptom

-5–6 points, moderate symptom

- 7 and above, severe symptom

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Statistical Analysis

The data was completed by being transferred to IBM SPSS Statistics for Windows (Version 23.0. Armonk, NY: IBM Corp.). The study data were assessed based on frequency distributions for categorical variables (number, percentage), and descriptive statistics for numerical variables (mean, standard deviation). Tiger Maier and Cox regression analysis were used to examine the factors affecting survival times. p <0.05 values were accepted as significant.

Ethical Approval

Ethics Committee approval for the study was obtained.

Results

The study included 52 patients with terminal-stage lung cancer with accessible data. The mean age of the patients was 62.25±9.39 years; and 43 (82.7%) were male and nine (17.3%) were female. Of the total, 43 (82.7%) were diagnosed with non-small cell lung cancer and nine (17.3%) with small-cell lung cancer. The majority of patients (67.3%) received systemic chemotherapy as the first-line therapy, and 28 (53.8%) had comorbidities (Table 1).

Of the total, 23 (44.2%) received morphine for dyspnea, 22 (42.3%) for pain, and seven (13.5%) for both. Morphine treatment was given IV to 29 (55.8%) patients and subcutaneously to 23 (44.2%) patients. The median dose administered to the patients

Table 1. Characteristics of Patients.

		N	%
Age		62,25±9,39	
Gender	Female	9	17,3
	Male	43	82,7
Pathology	Adenocarcinoma	32	61,5
	KHAK	9	17,3
	SCC	8	15,4
	NOS	3	5,8
Stage	3	8	15,4
	4	44	84,6
Comorbidity	None	24	46,2
	Available	28	53,8
Treatment	Chemotherapy	35	67,3
	Chemoradiotherapy	11	21,2
	Target-spesific therapy	2	3,8
	Immunotherapy	2	3,8
	Best Support Care	1	1,9
	Surgical	1	1,9
Morphine indication	Dyspnea	23	44,2
	Pain	22	42,3
	Dyspnea+Pain	7	13,5
Morphine application	IV	29	55,8
	SC	23	44,2
Dose (mg)		30,58±17,31	
Psychiatric drug	None	34	65,4
	Available	18	34,6
Non-morphine opioids	No	18	34,6
	Fentanyl	8	15,4
	Tramadol	26	50

SCC; Scuamous cell carcinoma, KHAK; Small cell carcinoma, IV; Intravenous, SC; Subcutaneous

Table 2. Examining the factors affecting survival times.

		Estimate	Std. Error	95% CI		p
				Lower Bound	Upper Bound	
Age	<65 years	86,772	19,141	49,256	124,288	0,867
	≥65 years	70,389	23,247	24,826	115,952	
	Overall	85,894	16,223	54,097	117,692	
Gender	Female	35,111	12,427	10,754	59,468	0,117
	Male	96,523	19,071	59,144	133,902	
Pathology	SCC	90	30,457	30,303	149,697	1-2 0,530 1-3 0,520 1-4 0,142 2-3 0,334 2-4 0,419 3-4 0,276
	Adenocarcinoma	82,578	20,406	42,583	122,574	
	NOS	156,333	63,834	31,219	281,448	
	KHAK	47,667	29,287	0	105,069	
Stage	3	174,625	52,807	71,124	278,126	0,051
	4	63,869	12,589	39,195	88,544	
Comorbidity	None	123,287	28,148	68,117	178,457	0,028*
	Available	50,286	13,58	23,668	76,903	
Morphine indication	Dyspnea	56,5	16,366	24,422	88,578	1-2 0,049* 1-3 0,754 2-3 0,074
	Pain	130,587	31,182	69,47	191,704	
	Dyspnea+Pain	38,714	12,626	13,967	63,461	
Morphine application	IV	73,701	19,829	34,835	112,567	0,543
	SC	88,652	21,429	46,652	130,652	
Dose (mg)	<60 mg	88,48	17,103	54,958	122,001	0,619
	≥60 mg	43,667	24,775	0	92,225	
Psychiatric drug	None	103,169	22,317	59,427	146,911	0,166
	Available	44,611	10,223	24,574	64,648	
Non-morphine opioids	No	92,722	26,631	40,526	144,919	1-2 0,529 1-3 0,509 2-3 0,961
	Fentanyl	69,125	31,533	7,321	130,929	
	Tramadol	75,865	19,748	37,16	114,571	

*p<0,05, SCC; Scuamous cell carcinoma, KHAK; Small cell carcinoma, IV; Intravenous, SC; Subcutaneous

Table 3. Examining the factors affecting survival times.

	B	SE	p	HR	95,0% CI	
					Lower	Upper
Comorbidity	0,653	0,306	0,033*	1,921	1,055	3,501

*p<0,05

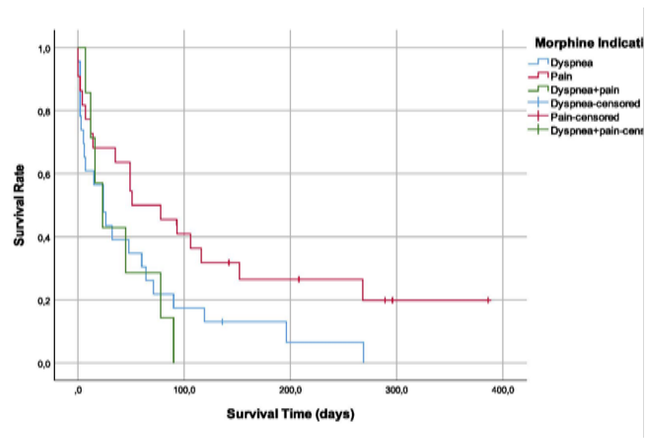

Figure 1. Survival curves of Morphine indication.

was 30.58±17.31 mg. Prior to the initiation of PMT, 18 (34.6%) patients were treated with psychiatric drug treatment, eight (15.4%) were treated with fentanyl for pain and 26 (50%) were on tramadol treatment (Table 1).

Patients whose dyspnea (shortness of breath) could not be relieved by any other method, including oxygen or sedative agents, and those whose pain symptoms could not be controlled with other treatments were started on parenteral morphine treatment.

In most cases, the starting dose was 0.2–0.4 mg/hour, equal to 5–10 mg/day, based on the decision of the physician and on the official statement of the American Thoracic Society [11]. The dose was increased to 0.2 mg/hour if symptoms did not improve.

The median dose of morphine was 27.7 mg in Group A, 31.8 mg in Group B, and 38.5 mg in Group C.

A good subjective response ("no symptoms" or "mild symptom") was documented in 46 patients (88.4%), poor response in four patients (7.4%) and no response in two patients (3.8%).

There was no change in the vital signs of the patients during the administration of the morphine, and no complications such as respiratory or cardiac depression were experienced. The main side effect was sedation.

The median survival time from the start of parenteral morphine treatment was 85.8 days across the entire patient group, while for the individual groups the mean survival time was 56.5 days in Group A, 130.5 days in Group B and 38.7 days in Group C. There was a statistically significant intragroup difference in survival time in those with pain indication ($p < 0.05$), with survival time being higher in patients with pain indication than in those with dyspnea indication (Figure1).

While there was no statistically significant difference in survival time associated with age, gender, pathology, stage, method of administration, dose (mg), psychiatric drug use and non-morphine opioids groups ($p > 0.05$), there was a statistically significant difference in terms of survival time in those with comorbidities ($p < 0.05$), with survival time being longer in patients without comorbidities than in those with comorbidities (Table 2).

The Cox regression analysis revealed that comorbidity status had a statistically significant effect on survival risk ($p < 0.05$), with the risk of death being 1.921 times higher in those with comorbidities than in those without comorbidities (Table 3).

Discussion

Opioids, including morphine and dihydrocodeine, are well known for their abilities in alleviating dyspnea by one or more mechanisms, including reducing the urge to breath and changing the central perception and activity of the peripheral opioid receptors located in the lung. Clinically, opioids have been shown to reduce anxiety [12,13].

In the present study, uncontrolled pain and shortness of breath in patients with terminal-stage lung cancer were considered indicators of parenteral morphine treatment, and the patients were divided into three groups accordingly: Group A (uncontrolled dyspnea), Group B (pain), Group C (both dyspnea and pain). In the study by Kim et al., a lower dose of morphine was given to patients with dyspnea, although life expectancy was determined to be shorter in this group than in the other studies groups [14]. In the present study, per the literature, it was found that a lower dose of morphine was required in patients with dyspnea, while the survival time from the onset of PMT was shorter in patients with dyspnea (Group B) than in patients without dyspnea (Group A or C).

The prevalence of dyspnea varies according to the primary tumor site. Shortness of breath is one of the most commonly reported symptoms in lung cancer, with 15% of patients applying with shortness of breath at the time of diagnosis, and 65% complaining of shortness of breath at some point in the course of their disease. Near their death, 90% of NSCLC patients suffer from shortness of breath [4]. In the present analysis, 30 (77.5%) of the patients received morphine treatment for the shortness of breath (Groups A and C).

Although few opioids are used in general, morphine continues to be the primary pharmacological treatment for dyspnea [15,16]. Although the use of opioids by clinicians is today approached with fear and suspicion, oral or parenteral opioid use is of vital importance in cancer-related shortness of breath, particularly in advanced stages of the disease, and in the first option for the treatment of dyspnea [17, 19].

There is, however, no standard dose, planning or administration route.

The efficacy of parenteral systemic morphine administration has been proven in cancer patients with dyspnea and pain [5,6,19,20].

Grond et al. [22] showed that morphine was more effective than tramadol.

In the present study, 29 (55.8%) of the patients received morphine IV and 23 (44.2%) subcutaneously, with the method of application being chosen by the physician. In a prospective study, continuous intravenous infusion and subcutaneous morphine have been shown to have similar effects and a similar side-effect profile [7].

Considering the advantages and disadvantages, the parenteral route is preferred, intravenous or subcutaneous [8]. In the present study, the subcutaneous or continuous infusion alternatives were applied depending on the severity of the symptoms of the patients, and no difference was detected in terms of efficacy and the side effect profile. The most common side effect in the present study was sedation, although we consider sedation to contribute to the relief of dyspnea. It is not clear whether morphine treatment shortens survival because we were unable to carry out a prospective study comparing prognosis within a placebo study.

Considering that all patients contacted had severe and resistant dyspnea, and there are no less risky treatment options, we believe the careful use of PMT under close observation to alleviate the symptoms of these patients to be ethically legitimate.

There is no established approach defining the optimum time to begin parenteral morphine treatment or increase the morphine dose. When differences in required morphine doses and survival times of the patient subgroups were taken into consideration in this study, it is apparent that the strategy may differ depending on the indications for parenteral morphine.

In conclusion, terminal-stage lung cancer patients require

parenteral morphine treatment to relieve the associated uncontrolled pain and shortness of breath, with the latter being the main indicator for morphine treatment. A lower dose of morphine than uncontrolled pain was required to relieve dyspnea, although those who required PMT due to dyspnea had a shorter life expectancy than those without dyspnea. Our results reveal PMT to be a safe and effective approach to the management of shortness of breath and pain in terminal cancer.

Limitations of our study include the retrospective study design and the small sample size.

Further studies are required to facilitate the effective and appropriate use of parenteral morphine treatments in end-stage lung cancer patients.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

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Conflict of interest

The authors declare no conflict of interest.

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